BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

REMARKS

Claim Amendments:

Claims 1, 27 and 38 have been amended to address the Examiner's concerns under 35 U.S.C. § 112, second paragraph. Specifically, these claims have been amended to clarify that the Markush group is modifying the carbohydrate polymer.

Claim 70 has been added to more particularly describe the present invention and to claim one of the preferred embodiments of the invention. Specifically, Claim 70 is identical to Claim 1 except that the term "mannose" has been substituted with the term "mannan". Support for this amendment is found in the specification on page 29, lines 13-19; and in the Examples section. It is submitted that the Examiner has already examined the claims to the extent necessary to examine new Claim 70 and that the addition of this claim will not require further searching or raise new issues.

Objection to the Specification and Rejection of Claims 13-16 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has maintained the rejection of Claims 13-16 under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner asserts that the specification does not present specific data for ensuring the antigenicity of claimed fragments that are 5 amino acids in length in such a way that an antigenic fragment of 5 amino acids would be predictably achieved. The Examiner contends that the prior art at the time of the invention predicts that a peptide that is 5 amino acids in length would not be antigenic because Class I MHC molecules would not accommodate 5 amino acid peptides.

Applicants traverse the rejection of Claims 13-16 under 35 U.S.C. § 112, first paragraph and submit that, contrary to the Examiner's contention that the prior art at the time of the invention predicts that Class I MHC molecules would not accommodate 5 amino acid peptides. It is respectfully noted that the Examiner has referenced a 1991 text in support of the position that the Class I MHC accommodates peptides that are 10-20 amino acids long. However, Applicants submit that prior to and at the time of the invention, it was well known in the art that Class I MHC molecules actually preferably bind peptides that are 8-9 amino acids in length and that Class I MHC molecules can indeed bind to peptides that are as small as 5 amino acids. In support of this position, Applicants have enclosed the Declaration under 37 CFR 1.132 of Dr. Geoffrey A. Pietersz. This

Declaration was not earlier presented because it is only in the February 13 Office Action that the Examiner asserted the reference regarding the alleged state of the art for MHC Class I peptide presentation, which Applicants have evidence to rebut.

More particularly, paragraph 4 of the Declaration provides literature support for the position that, at the time of the present invention, it was known that Class I MHC molecules preferably bind peptides that are 8-9 amino acids in length and that Class I MHC molecules can bind peptides as small as 5 amino acids (see paragraphs 4(b)-4(c)). Applicants note that for the Eisen *et al.* reference identified in paragraph 4(b), only a printout of the PubMed database entry is attached. Applicants will submit in a supplemental response either a substantive excerpt of the article or the full article. Moreover, the Declaration provides evidence that cytotoxic T lymphocytes (CTLs) are capable of recognizing target RMA-S cells (i.e., via Class I MHC presentation) that present MUC1 peptides between 5 and 9 amino acids in length (see paragraph 4(a)) and that an 8-mer peptide mimic of MUC1 is capable of inducing CTL responses (see paragraph 4(d)). Finally, paragraph 4(e) attests to the immunogenicity of the aldehyde groups in the antigen-carbohydrate polymer conjugate of the invention, such that one of skill in the art would expect that peptides as small as 5 amino acids provided in accordance with the claimed composition would be presented by MHC Class I and would be immunogenic.

In summary, Applicants submit that the specification, in combination with the knowledge in the art at the time of the invention regarding Class I MHC peptides and the additional support provided by the Declaration under 37 CFR 1.132, provides sufficient guidance to the skilled artisan to determine whether a given peptide fragment is antigenic, and in particular, whether such fragment can bind to MHC and in this context, elicit a cellular immune response.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 13-16 under 35 U.S.C. § 112, first paragraph.

Objection to the Specification and Rejection of Claims 1, 3-21, 23-34, 36-45 and 47-51 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has maintained the rejection of Claims 1, 3-21, 23-34, 36-45 and 47-51 under 35 U.S.C. § 112, first paragraph, contending that there would be an unpredictable amount of

experimentation required to practice the claimed invention, because the specification allegedly does not provide sufficient guidance to provide a conjugate containing any carbohydrate polymer with one mannose. The Examiner notes that the specification exemplifies a conjugate comprising mannan, but contends that it would require undue experimentation to practice the claimed method of gene therapy.

As for this last statement regarding gene therapy, Applicants assume that this is a typographical error, since the invention is not directed to gene therapy. However, Applicants traverse the Examiner's contention that undue experimentation would be required of one of skill in the art to provide an immunoregulatory composition comprising a conjugate containing any carbohydrate polymer with one mannose. In support of the position discussed below, the Declaration under 37 CFR 1.132 of Dr. Geoffrey A. Pietersz provides comments and evidence that a conjugate containing even one mannose would be expected to be immunostimulatory in a composition according to the present invention.

First, Applicants again submit that, using the guidance provided in the specification, one of skill in the art would be able to produce the claimed composition, including a conjugate containing a carbohydrate polymer comprising mannose. As set forth in paragraph 5 of the Declaration, and in the specification, pages 28-32, the skilled artisan would readily be capable of first synthesizing a backbone chain wherein the carbohydrate monomers may include mannose and any one or a mixture of carbohydrate monomers such as those disclosed on page 28, lines 1-10 of the present specification, followed by activating and conjugating the polymer to an antigen as disclosed at pages 28, line 16 to page 32, line 9. Given the state of the art in protein chemistry and molecular biology, Applicants submit that it is not necessary for the specification to present specific data for all carbohydrate polymers containing at least one mannose in order to enable the skilled artisan to produce such a composition. The exemplification of a carbohydrate polymer containing mannan, in combination with the other guidance in the specification, is sufficient to teach the skilled artisan how to produce the claimed compositions using any carbohydrate polymer.

Second, Applicants submit that one of skill in the art would predictably be capable of producing a conjugate according to the present invention that contains a carbohydrate polymer comprising at least one mannose with the expectation that such conjugate would be

immunostimulatory. As set forth in the previous response, the inclusion at least one mannose subunit in the polymer, in addition to being a carrier for the antigen, allows the conjugate to bind to and be internalized, processed and presented by a *mannose-receptor bearing cell* of the present invention. Applicants have already addressed the contribution of the antigen and the aldehyde groups to the immunostimulatory effect of the conjugate (e.g., see Paragraph 4(e) of the Declaration). As set forth in the Declaration (see paragraph 5), even one mannose can bind to a mannose receptor present on, for example, macrophages and dendritic cells, thereby stimulating an immune response as demonstrated in the present specification. The Declaration provides data showing that a conjugate containing mannose can compete with free mannose for binding to mannose receptors, and that this is the mechanism by which the conjugate enters the cell and the MHC Class I pathway. Therefore, by including at least one mannose in the carbohydrate polymer portion of the claimed composition, one of skill in the art can predictably produce the immunoregulatory composition of the present invention, without undue experimentation.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-21, 23-34, 36-45 and 47-51 under 35 U.S.C. § 112, first paragraph.

Rejection of Claim 1 and Dependent Claims 2-19 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claim 1 and dependent claims 2-19 under 35 U.S.C. § 112, second paragraph. Specifically, the Examiner contends that it is unclear whether the Markush group in Claim 1 refers to the mannose or to the carbohydrate polymer.

Applicants have amended Claim 1, as well as similarly worded independent Claims 27 and 38, to clarify that the Markush group is referring to the carbohydrate polymer.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-19 under 35 U.S.C. § 112, second paragraph.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment.

Applicants have attempted to address the Examiner's concerns as set forth in the February 13, 2001 Office Action. In the event that the Examiner has any questions or concerns regarding Applicants' position, the Examiner is invited to contact the below named attorney at (303) 863-9700.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: _____

Gary J. Connell
Registration No. 32,020
1560 Broadway, Suite 1200
Denver, Colorado 80202-5141
(303) 863-9700

Date: 11 May 2001

Marked-up Version Showing Amendments

Claims 1, 27 and 38 have been amended as shown below.

Claim 70 has been added.

All other pending claims remain unchanged.

1. (Twice Amended) An immunoregulatory composition comprising isolated mannose receptor-bearing cells and a conjugate comprising an antigen and a carbohydrate polymer comprising mannose, wherein said carbohyrate polymer is selected from the group consisting of fully oxidized [mannose] carbohydrate polymer comprising free aldehydes and partially reduced [mannose] carbohydrate polymer having aldehydes.

27. (Twice Amended) An immunoregulatory mannose receptor-bearing cell population, wherein said immunoregulatory mannose receptor-bearing cell population can be derived by a method comprising:

a) culturing mannose receptor-bearing cells *in vitro* with one or more biological response modifiers to produce an enhanced mannose receptor-bearing cell population; and

b) incubating said enhanced mannose receptor-bearing cell population with a conjugate comprising an antigen and a carbohydrate polymer comprising mannose, wherein said carbohyrate polymer is selected from the group consisting of fully oxidized [mannose] carbohydrate polymer comprising free aldehydes and partially reduced [mannose] carbohydrate polymer having aldehydes, to obtain said immunoregulatory mannose receptor-bearing cell population.

38. (Twice Amended) A mucin antigen delivery vehicle, comprising an isolated mannose receptor-bearing cell and a conjugate comprising mucin antigen and a carbohydrate polymer comprising mannose, wherein said carbohyrate polymer is selected from the group consisting of

fully oxidized [mannose] carbohydrate polymer comprising free aldehydes and partially reduced [mannose] carbohydrate polymer having aldehydes.

Claim 70 has been added, as follows.

70. (Added) An immunoregulatory composition comprising isolated mannose receptor-bearing cells and a conjugate comprising an antigen and a carbohydrate polymer comprising mannan, wherein said carbohyrate polymer is selected from the group consisting of fully oxidized carbohydrate polymer comprising free aldehydes and partially reduced carbohydrate polymer having aldehydes.